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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,836	09/17/2003	Zhi-Xian Wang	PT-2050000	2694

23607 7590 12/01/2005

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EXAMINER

OH, TAYLOR V

ART UNIT

PAPER NUMBER

1625

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/663,836

Applicant(s)

WANG ET AL.

Examiner

Taylor Victor Oh

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 35 is/are allowed.
- 6) ☒ Claim(s) 1-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/22/04</u> . | 6) <input type="checkbox"/> Other: _____ |

The Status of Claims

Claims 1-35 are pending.

Claims 1-34 have been rejected.

Claim 35 has been allowed.

DETAILED ACTION

Priority

1. None .

Drawings

2. None.

Specification

The disclosure is objected to because of the following informalities in the specification (see page 3 , lines 3-8) :

- 1) begins from the inexpensive and readily available 2-halobenzoic acid
- 2) high selectivity in the halogenation and amide formation steps
- 4) high yield
- 5) low cost solvents used throughout
- 6) amenable for large scale production and does not require specialized equipment.

Among the steps, there are no commas and there is no conjunction " and " before the step (6). Appropriate correction is required.

Claim Objections

Claim 4 is objected to because of the following informalities:

In claim 4, the phrases

"R² is C₁ to C₉ alkyl group, aryl group or succinimidyl " and

"

selective amide formation by reacting compounds of formula VI or VII with 2-(aminomethyl)piperidine forming flecainide base;

" are recited. There is no punctuation between them.

. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-8, 11-23, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enable for a catalyst ,such as palladium and nickel,

**cupric chloride, cupric bromide, cupric iodide, cuprous chloride, cuprous bron
cuprous iodide, copper (I) oxide, copper (II) oxide or copper-zinc alloy.**

The catalyst claim does not reasonably provide enablement for all the catalyst known in the chemical art. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to include the catalyst unrelated to the invention commensurate in scope with these claims.

Furthermore, the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation.**

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation, citing *Ex Parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,

- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

In the instant case, the claim encompasses various catalysts. However, applicants' specification provide only one particular exemplified catalyst (cupric bromide); the group of the catalyst employed is directed to the very specific reaction process in the claimed invention: in addition, the catalyst compositions represent an unpredictable aspect in the art of organic chemistry . See *Exparte Sizto*, 9 USPQ2d 2081 (Bd. Of App. And Inter. March 1988). Thus, the specification herein have failed to provide sufficient working examples to support the use of various catalysts. Therefore, an appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the formula VI is converted

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to the ester of formula VII; how the compound of formula VI or VII is converted to the flecainide base.

Claims 8-10, 23-25, and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 8 and 23, the phrase "a base selected from potassium tert-butoxide, sodium tert-butoxide, sodium isopropoxide or sodium methoxide" is recited. The conjunction "or" is improper in the claimed sentence because the claimed phrase "a base selected from " leaves the claim close for any inclusion. Therefore, an appropriate correction is required.

In claims 9, 10, 24, and 25, the phrases "a copper type catalyst" and "the like " are recited. The terms "type " and "the like " are vague and indefinite because the specification does not elaborate what is meant by each of the "type " and "the like ". Therefore, an appropriate correction is required.

Claims 28-30 recite the limitation " (the) solvent(s) " in claim 27. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27-29, 31, and 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Mcdaniel et al (WO 02/066413) .

Mcdaniel et al discloses

(f) Preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)-benzamide (V):

2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy) benzoate (50 g, 0.125 mole) in 100 mL glyme was added, over about 40 minutes, to a colorless solution of 2-

aminomethylpyridine (16.2 g, 0.15 mole) in 100 mL of glyme. The mixture was stirred under a dry nitrogen atmosphere at about 20 to 25 °C. The resulting solution was stirred for about 20 hours at about 20° to 25 °C, then stirred with heating to gentle reflux for about 3 hours. The solution was cooled to 20° to 25 °C and then concentrated *in vacuo* to a volume of 75 mL. Hexane (500 mL) was added with stirring at about 20° to 25 °C in 1 hour. The resulting slurry was stirred at about 20 to 25 °C for 4 hours and then filtered. The collected solids were washed with hexane (100 mL) and the product dried in air at constant weight. The amide (V) was obtained as an off-white powder (50 g, 99% yield), melting point 101-103 °C. (see from page 17, line 29 to page 18, line 8).

This identical with the claims.

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Claims 27-28, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by Banitt et al (US 4,005,209) .

Banitt et al discloses the preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride shown below (see col. 10 ,lines 1-25):

Under a nitrogen atmosphere 2-aminomethylpiperidine (0.249 mole, 28.4 g.) is treated dropwise over 25 minutes with 2,2,2-trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (0.0249 mole, 10.0 g.). After 3 hours 50 ml. of benzene is added to the thick mixture and stirred for about 40 hours, at 45° C. The mixture is then concentrated under vacuum with heating to remove the volatile components. The residue solidifies after cooling, is steam distilled for further purification and is separated by filtration and extracted into dichloromethane. The dichloromethane solution is washed with saturated sodium chloride solution, and the organic layer is dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration and 4 ml. of 8.4 N hydrogen chloride in isopropanol is added to the dichloromethane solution with stirring. After two hours the mixture is cooled to about 0° C. and the crude product is collected by filtration, washed with diethyl ether and dried in a vacuum oven. After treatment with decolorizing charcoal and recrystallization from an equivolume mixture of isopropanol and methanol, the product, 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride, has a melting point of 228°-229° C.

This identical with the claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 27-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mcdaniel et al (WO 02/066413) in view of Banitt et al (US 4,005,209).

Mcdaniel et al discloses

(f) Preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)-benzamide (V):

2,2,2-Trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy) benzoate (50 g, 0.125 mole) in 100 mL glyme was added, over about 40 minutes, to a colorless solution of 2-aminomethylpyridine (16.2 g, 0.15 mole) in 100 mL of glyme. The mixture was stirred under a dry nitrogen atmosphere at about 20 to 25 °C. The resulting solution was stirred for about 20 hours at about 20° to 25 °C, then stirred with heating to gentle reflux for about 3 hours. The solution was cooled to 20° to 25 °C and then concentrated *in vacuo* to a volume of 75 mL. Hexane (500 mL) was added with stirring at about 20° to 25 °C in 1 hour. The resulting slurry was stirred at about 20 to 25 °C for 4 hours and then filtered. The collected solids were washed with hexane (100 mL) and the product dried in air at constant weight. The amide (V) was obtained as an off-white powder (50 g, 99% yield), melting point 101-103 °C. (see from page 17, line 29 to page 18, line 8).

However, the instant invention differs from the prior art in that the claimed toluene solvent is disclosed for the process at a reaction temperature between 50 to 120° C .

Banitt et al discloses the preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride shown below (see col. 10 ,lines 1-25):

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Under a nitrogen atmosphere 2-aminomethylpiperidine (0.249 mole, 28.4 g.) is treated dropwise over 25 minutes with 2,2,2-trifluoroethyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (0.0249 mole, 10.0 g.). After 3 hours 50 ml. of benzene is added to the thick mixture and stirred for about 40 hours at 45° C. The mixture is then concentrated under vacuum with heating to remove the volatile components. The residue solidifies after cooling, is steam distilled for further purification and is separated by filtration and extracted into dichloromethane. The dichloromethane solution is washed with saturated sodium chloride solution, and the organic layer is dried over anhydrous magnesium sulfate. The magnesium sulfate is removed by filtration and 4 ml. of 8.4 N hydrogen chloride in isopropanol is added to the dichloromethane solution with stirring. After two hours the mixture is cooled to about 0° C. and the crude product is collected by filtration, washed with diethyl ether and dried in a vacuum oven. After treatment with decolorizing charcoal and recrystallization from an equivolume mixture of isopropanol and methanol, the product, 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide hydrochloride, has a melting point of 228°-229° C.

With respect to the use of toluene solvent in the claimed process, Banitt et al does teach that it is possible to use the benzene solvent similar to the toluene for the process ; they are commonly known as hydrocarbon solvents; they have shared a similar physical and chemical property due to being a homologue to each other. Furthermore, it is well- established that the substitution of methyl for hydrogen on known compound is not a patentable modification absent unexpected or unobvious results. In re Wood, 582 F. 2d 638, 199 USPQ 137 (C.C.P.A. 1978); In re Hoke, 560 F.2d 436, 195 USPQ 148 (C.C.P.A. 1978). Therefore, it would have been obvious to the skilled artisan in the art to be motivated to use the toluene solvent as an alternative to the

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benzene. This is because the skilled artisan in the art would expect such a modification to be successful in the absence of unexpected or unobvious results.

Regarding the temperature difference, the claimed ranges and the prior art do not overlap but are close enough that one skilled in the art would have expected them to have the same properties in the absence of unexpected results. Furthermore, The limitation of a process with respect to ranges of pH, time and temperature does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art in achieving optimum operation of the process. Temperature is well understood by those of ordinary skill in the art to be a result-effective variable, especially when attempting to control selectivity in a chemical process. Therefore, it would have been obvious to the skilled artisan in the art be motivated to optimize the reaction temperature by routine experimentation in order to achieve the claimed process.

Both prior art commonly teach the preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide by reacting 2,2,2-trifluoroethoxyl 2,5-bis (2,2,2-trifluoroethoxy)benzoate with 2-aminomethylpiperidine. Banitt et al does teach that it is possible to use the benzene solvent similar to the toluene for the process since they have a similar role as the hydrocarbon solvent. Furthermore, it is well-established that the substitution of methyl for hydrogen on known compound is not a patentable modification absent unexpected or unobvious results. In re Wood, 582 F. 2d 638, 199

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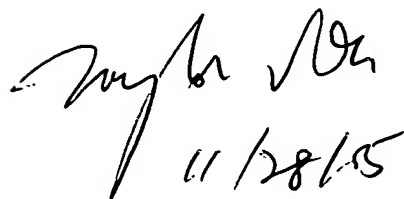
USPQ 137 (C.C.P.A. 1978); In re Hoke, 560 F.2d 436, 195 USPQ 148 (C.C.P.A. 1978).

Therefore, it would have been obvious to the skilled artisan in the art to be motivated to use the toluene solvent as an alternative to the Banitt's et al benzene solvent in the Mcdaniel et al process. This is because the skilled artisan in the art would expect such a modification to be successful as shown in the Banitt et al process .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


11/28/15